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Review Article

Preventing coronary artery lesions in Kawasaki disease

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ARTICLE INFO

Article history:

Received 25 January 2017

Accepted 27 April 2017

Available online 30 May 2017

Keywords:

Kawasaki disease

Coronary artery lesion

Prevention

ABSTRACT

A form of systemic vasculitis that affects mostly small and medium-sized vessels, Kawasaki disease (KD) is most commonly found in children under the age of 5 years old. Though its etiology is unknown, KD has been the most frequent acquired heart disease in developing countries. Its incidence has increased over recent decades in many countries, including Japan, Korea, and China. The most severe complications of KD are coronary artery lesions (CAL), including dilation, fistula, aneurysm, arterial remodeling, stenosis, and occlusion. Aneurysm formation has been observed in 20–25% of KD patients that do not receive intravenous immunoglobulin (IVIG) treatment, and in 3–5% that do receive it. Coronary artery dilation has been found in about 30% of KD patients in the acute stage, although mostly in the transient form. Diminishing the occurrence and regression of CAL is a vital part of treating KD. In this review article, I demonstrate the clinical method to prevent CAL formation used at the Kawasaki Disease Center in Taiwan.

Kawasaki disease (KD) is recognized as the most frequent acquired heart disease in children. Dr. Kawasaki et al. first described this acute febrile systemic vasculitis in Japan in 1967 [1]. It mainly affects children under the age of 5 years old, especially those in such Asian countries as Japan, Korea, Taiwan, and China. As a form of systemic vasculitis, KD has been reported to predominantly involve small to medium-sized vessels. The most severe complication or sequela is the formation of coronary artery lesions (CAL), such as myocardial infarction, coronary artery fistula [2], coronary artery dilatation, and coronary artery aneurysm, which may subsequently result in long-term sequelae like stenosis or obstruction and myocardial infarction [3]. The etiology of KD

continues to be unknown [4–6], but it has demonstrated an increasing incidence worldwide, particularly in Japan. However, this increase has not been significant in Taiwan [7–10].

KD may be caused by a combination of genetic background (CD40, BLK, ITPKC, FCGR2A, CD40L, CASP3 ... etc.) [11–22], infectious agents (bacteria, virus, mycoplasma, etc.) [6,23] and immune response [24,25]. The standard treatment for KD is high-dose aspirin (80–100 mg/kg/day) and high-dose intravenous immunoglobulin (IVIG, 2 g/kg), which have been shown to significantly decrease the rate of coronary artery aneurysms from 20–25% to 3–5% [26,27]. While a single high dose of IVIG has been found to be more effective than four smaller daily doses or two daily doses with the same

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Peer review under responsibility of Chang Gung University.

<http://dx.doi.org/10.1016/j.bj.2017.04.002>

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accumulation dosage [5], the effectiveness of IVIG for treating KD is still under investigation. FCGR2A may be the answer from genome-wide association study (GWAS) and methylation array results [15,28]. Hypomethylation of CpG sites in the FCGR2A promoter region were reported to be related to KD susceptibility and IVIG resistance; mRNA gene expression confirmed such findings. FCGR2A is over expressed in the acute stage and then subsides to the same range once controlled, which may indicate the treatment efficacy of IVIG in KD patients, as well as the possible role of purified Fc portion products in future KD treatments [15,28].

While IVIG treatment significantly decreases the occurrence of coronary artery aneurysm formation, about 1/3 of KD patients will still develop coronary artery dilation in the acute stage. In our previous reports, using a serial analysis of coronary artery dilation (n = 341) [29], 35% of KD patients experienced dilatation in the acute stage, 17.2% noted dilatation one month after the onset of the disease, 10.2% still had dilatation two months after the onset of the disease, and 4% had CAL or aneurysm formation for at least one year. Identifying KD during the 5–10 days of disease onset is very important, as is treating KD with a more precise protocol, especially for those children with IVIG resistance, in a high-risk group, or with CAL formation. In this article, I demonstrate the clinical practice of preventing CAL formation adopted by the Kawasaki Disease Center in Taiwan.

How to diagnose typical and atypical Kawasaki disease

Clinical diagnosis criteria (Kuo Mnemonic: 1–2–3–4–5)

The clinical characteristics of KD include fever lasting for more than 5 days, as well as at least four of the following five symptoms: diffuse mucosal inflammation with strawberry tongue and fissure lips (1 mouth), bilateral non-purulent conjunctivitis (2 eyes), unilateral cervical lymphadenopathy (3 fingers check lymph node), indurative angioedema over the hands and feet (4 limbs), dysmorphic skin rashes (5 or more skin rashes) [5]. These five KD characteristic symptoms may not be easy to remember for parents or first-line clinicians. Finding an easier technique for remembering the five characteristics of KD is important for both parents and clinicians so that KD can be identified earlier. In order to help with that, I created the “Kuo Mnemonic” to quickly recall KD diagnosis criteria [Table 1], which has been modified from our previous

review [25]. According to the Japanese Circulation Society Joint Working Groups' criteria (JCS 2008, Guidelines for diagnosis and management of cardiovascular sequelae in KD) [30], KD can be diagnosed even when a fever occurs for less than 5 days. However, according to the American Heart Association (AHA) criteria (3), a fever lasting for 5 days or more is essential for a diagnosis of KD.

Bacillus Calmette-Guérin (BCG) site induration

In countries with a routine BCG immunization policy (such as Taiwan and Japan), an erythematous change over BCG scars will be observed in one-third to one-half of KD patients [4]. Tseng et al. reported that this bull's eye dermatoscopic sign is not only a useful diagnostic marker but can also serve as a severity biomarker of CAL formation in KD patients [31]. Furthermore, Uehara et al. [32] reported that redness or the formation of a crust at the BCG inoculation site is a useful sign for diagnosing KD in children. In Taiwan, the BCG vaccine schedule was changed in year 2016 to 5 month-old of age, this diagnostic sign of BCG induration cannot be used for children younger than 5 months old suspecting of having KD.

If a patient has 4 or fewer signs of the KD clinical criteria, physicians should consider redness or crust formation at the BCG inoculation site as a possible indicator of KD. Altogether, a BCG site induration change can serve as independent diagnostic criteria to help diagnose KD. If patients are suspected of having KD but do not fully fit the diagnosis criteria, the physician should further consider BCG vaccination site indurations, as well as the six items of AHA supplemental criteria for KD, consulting a KD expert, and ordering a cardiac echography [Table 2].

Consulting a Kawasaki disease expert

A KD expert (such as a cardiologist, immunologist, infectious disease specialist, or rheumatologist) should be consulted when fever lasts for ≥ 7 days without a definitive diagnosis. The major diagnostic criteria of KD depend on five clinical symptoms, which causes diagnosis to be subjective. No laboratory data (objective markers) are currently available to be used specifically for diagnosing KD. Consulting an expert will improve the subjectivity of making diagnosis for KD. The website *Expertscape* provides a good way to find KD experts throughout the world and can be searched according to city, area, country, and continent (www.expertscape.com).

Table 1 Rapid memory method of “Kuo Mnemonic” for Kawasaki disease diagnostic criteria.

Number	Mnemonic method	Clinical symptoms and signs
1	“One” mouth (humans have 1 mouth)	Diffuse mucosal inflammation with strawberry tongue and fissure lips
2	“Two” eyes (humans have 2 eyes)	Bilateral non-purulent conjunctivitis
3	“Three” fingers palpation neck lymph nodes (Doctors use 3 fingers to check neck for lymph nodes)	Neck lymphadenopathy (unilateral, >1.5 cm)
4	“Four” limbs changes (humans have 4 limbs)	Indurative over hands and feet (peeling in subacute stage)
5	“Five” = multiple skin rashes (5 indicates a lot)	Dysmorphic general skin rashes

*This table was modified from previous report [25].

Table 2 Evaluation of patients suspected of having Kawasaki disease.

Fever	Major symptoms		Treatment
<5	4	Follow daily	Not IVIG (when without CAL)
<5	5	Treatment by JCS but not AHA	Possible IVIG
≥5	5	2D + KS	IVIG
≥5	4	2D + KS	IVIG
≥5	3 + BCG	2D + KS	IVIG
≥7 (in 6-month-olds)	0	2D + SLC + consult expert	Possible IVIG
≥7	2–3	2D + SLC + consult expert	IVIG when positive
>10	2–3	2D + SLC + consult expert	IVIG when positive

Abbreviations: 2D: cardiac echography; SLC: Supplemental laboratory criteria; KD: Kawasaki disease; CAL: coronary artery lesions; JCS: Japanese Circulation Society Joint Working Groups [30]; AHA: American Heart Association [3].

Kobayashi score (KS): A 7-variable logistic model was constructed, including day of illness at initial treatment, age in months, percentage of white blood cells representing neutrophils, platelet count, and serum aspartate aminotransferase, sodium, and C-reactive protein [46].

AHA supplemental criteria

The AHA and American Academy of Pediatrics (AAP) released the KD supplemental laboratory criteria in 2004 for patients suspected of having KD but with an incomplete diagnosis, which included the following six components: (1) urine ≥ 10 white blood cells/high-power field; (2) albumin ≤ 3.0 g/dL; (3) elevation of alanine aminotransferase; (4) platelet count $\geq 450,000/\text{mm}^3$ after 7 days of fever; (5) total white blood cell count $\geq 15,000/\text{mm}^3$; and (6) anemia by age [3]. If a patient meets more than three of the supplementary criteria, incomplete KD can be diagnosed, and IVIG should be prescribed before arranging for echocardiography [3].

Treating Kawasaki disease and IVIG resistance with precision medicine

IVIG

IVIG has been used as a treatment for KD since it was first prescribed in 1983 by Furusho et al. [33]; that was more than 15 years after KD was originally reported in 1967. Later, in 1986, Newburger et al. [27] found that high-dosage IVIG (400 mg/kg/day for 4 days) was a safe and effective treatment for reducing the prevalence of coronary artery aneurysm formation from 20–25% to 3–5%. In 1991, a single high dose of IVIG (2 g/kg) was reported to be more effective than the four-day regimen [34]. A single high dose of IVIG (2 g/kg in 10–12 h infusion) and high-dose aspirin (80–100 mg/kg/day) are currently considered the gold standard for treating KD. IVIG treatment should not be spread out over 24 h, 2 days, or 4 days.

A single high dose (2 g/kg) of IVIG administered through a 10–12-h infusion course within 5–10 days of disease onset is the most effective treatment for KD right now.

Aspirin

Aspirin has been used to treat KD for more than 40 years, even before IVIG began being prescribed in 1983. While aspirin has important anti-inflammatory (high dose) and anti-platelet (low dose) functions, it does not appear to reduce the occurrence of CAL formation. During acute-phase KD, aspirin is administered at 80–100 mg/kg per day (30–50 mg/kg in Japan) [35] in four doses. Hsieh et al. [35] reported that high-dose

aspirin in the acute stage of KD does not affect the response rate of IVIG therapy, duration of fever, or incidence of CAL when children are also treated with a single infusion of high-dose (2 g/kg) IVIG. In fact, exposing children with acute KD to high-dose aspirin therapy may be unnecessary, especially since the available data has shown no substantial benefit with regard to preventing the failure of IVIG therapy, CAL formation, or shortening fever duration. In our recent report, administering high-dose aspirin in acute-stage KD does not provide any benefits with regard to inflammation markers (C-reactive protein, hepcidin, and hemoglobin levels) [36]. The use of high-dose aspirin in the acute stage of KD still needs multi-center randomized controlled trials before a conclusive determination can be reached. Thereafter, 48–72 h after the fever subsides, dosage can be reduced to 3–5 mg/kg/day and should be continued for at least 6–8 weeks after disease onset till normalization of CAL.

IVIG resistance (non-responsiveness or failure)

Since IVIG-resistant patients are at a higher risk for CAL formation, identifying those that may benefit from a more aggressive therapy is important. A second dose of IVIG (2 g/kg) [3,37], methylprednisolone pulse therapy [38], tumor necrosis factor- α blockade [39], cyclophosphamide, cyclosporine A, methotrexate [40], plasmapheresis [41], and plasma exchange [42] have all been reported to benefit KD patients whose initial IVIG treatment had failed. A single-pulsed dose of intravenous methylprednisolone (IVMP, 30 mg/kg with a maximum dose of 1000 mg) combined with IVIG compared to IVIG therapy alone does not significantly improve disease outcome when used as the primary treatment for children with KD [43]. Though IVMP appears to not add treatment value when combined with IVIG for initial treatment and the mechanism is still unknown (our preliminary results suggest that it may be associated with decreased steroid receptor expression in acute-stage KD, data not shown), IVMP therapy over a 3-day course of treatment seems to benefit IVIG-resistant KD patients [37]. In Kaohsiung Chang Gung Memorial Hospital in Taiwan, I used a secondary course of high-dose IVIG (2 g/kg in 10–12 h) for initial IVIG-resistant KD patients; then I prescribed IVMP (30 mg/kg/day, for 3 days) for continued IVIG resistance in the secondary dose; and then I prescribed anti-TNF- α agent for continued resistance to IVMP.

Although the incidence of KD has increased in the past decades, the incidence of recurrent KD has remained largely unchanged over the past 30 years in Japan (3.89–6.51 per 1000 person-years). Risk factors for recurrence KD included male sex, young age and IVIG resistance [44].

Preventing coronary artery lesion formation

Treatment for KD patients with a proper dosage of IVIG (a single high dose of 2 g/kg of body weight) in the proper duration of 10–12 h infusion [5], prescribed within the first 5–10 days of the illness will more effectively reduce CAL formation [3]. Treating KD before day 5 of the illness seems no more likely to prevent CAL than dose treatment after day 5 of the illness, but it may be correlated with an increased need for another course of IVIG treatment. However, if KD patients are found to have CAL formation even before the 5th day from the onset of the disease, IVIG should then be given prior to the first AHA criteria for KD of fever for more than 5 days. IVIG should also be administered to KD patients presenting after the 10th day of illness (i.e., children in whom the diagnosis was missed earlier) if they have either ongoing systemic inflammation according to their elevated erythrocyte sedimentation rate (ESR) or CRP and persistent fever without other explanation or aneurysm formation.

Echocardiography should be considered for patients who were suspected to have KD with peeling (or even those not) at admission but did not meet the diagnostic criteria after they are discharged from the hospital. For patients with severe KD or those in a high-risk group, Kobayashi et al. suggested that adding prednisolone to IVIG could significantly improve coronary artery outcomes [45]. The Kobayashi score provides a good tool for predicting CAL formation, so prednisolone may be effective in regression of CAL in those KD patients who already have CAL formation [46]. Further investigation is required before reaching a definite conclusion. Salgado et al. reported that despite treatment in the first 10 days, infants <6 month-old of age with acute KD are more likely to develop CAL. Thus, adjunctive anti-inflammatory therapies to reduce CAL should target this population [47].

Other off-label treatments

No treatment differences were found between KD patients with CAL formation and those without CAL formation in acute stage and after discharged. Maybe only low-dose aspirin is prescribed for KD patients after the fever subsides, regardless of CAL formation. Patients with KD may be classified into different groups according to disease severity including KD shock syndrome, KD with giant aneurysm formation, KD with aneurysm formation, KD with coronary artery dilation, KD with transient coronary artery dilation, KD with IVIG resistance, KD without CAL nor IVIG resistance. Among these groups of KD, different treatment protocol maybe needed as the spirit of precision medicine.

Dextromethorphan (DM) is a dextrorotatory morphinan that has been widely used as a nonopioid cough suppressant for decades, although the exact mechanism remains unclear. Interestingly, previous studies using animal models of

cerebral ischemia and hypoglycemic neural injuries have demonstrated the neuroprotective activity of DM, which may be related to its effects on NADPH oxidase since DM may effectively prevent the production of reactive oxygen species (ROS) induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Low-dose DM was reported to reduce blood pressure and enhance vascular protection in experimental hypertension [48]. TNF-alpha, which potentiates ROS generation, is vital factor for the development of CAL formation in KD. The vascular NADPH oxidase enzyme was reported to participate in TNF-alpha-triggered endothelial damage by elevating ROS generation [49]. Ultimately, DM, in addition to low-dose aspirin, may benefit KD patients with CAL formation.

Promoting Kawasaki disease awareness

A prolonged fever with some respiratory or gastrointestinal tract symptoms and will affect the heart, these are the characteristics of KD that confuse parents when visiting the clinic or hospital. Cardiologists, infectious disease specialists, rheumatologists, and even urologists may care for KD patients in the acute stage of the disease. A KD outpatient clinic (OPD) is a good way to decrease the family's confusion during visits and follow-ups.

Books aimed at parents will help raise awareness of KD, making it easier to face the disease if they ever have to. I have published three books about KD in Chinese in Taiwan. The first is a more detailed book that describes immune mechanisms, images, genetic findings, infectious association, treatment, follow-up and questions/answer from parents. The second book is a more approachable edition that included the rapid memory method (1 mouth-2 eyes-3 fingers palpable neck lymphnode-4 limbs change-5 skin rashes) [25] for diagnosis criteria and many characteristic photos of KD to help parents more easily identify this disease. The third book is particularly aimed at parents who have already had children with KD, and the content includes pharmacology, rehabilitation, psychiatry, nursing, social work, nutrition, traditional Chinese medicine, and allergies.

Conclusion

Increasing KD awareness with the rapid memory methods of the Kuo Mnemonic, early diagnosis (through echocardiography, supplemental criteria, and BCG induration), precise treatment (IVIG, 2nd dose IVIG, IVMP, anti-TNF-alpha) and precision medicine (steroid or dextromethorphan or other anti-inflammatory agents) will all help diminish the coronary artery damage from KD.

Conflicts of interest

The author has no conflicts of interest to declare.

Acknowledgement

This study was supported by grants provided by the Ministry of Science and Technology (MOST: 105-2314-B-182-050-MY3), and Chang Gung Memorial Hospital (CMRPG8F1911, CMRPG8E1612, CMRPG8E0212 and CORPG8F0012) in Taiwan.

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